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SUMMARY WITH CRITICAL APPRAISAL

Buprenorphine Formulations for the Treatment of Opioid Use Disorders: A Review of Comparative Clinical Effectiveness, Cost-Effectiveness and Guidelines

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Context and Policy Issues

Opioid use disorder (OUD) is known to be a chronic, relapsing illness which is associated with high rates of morbidity and mortality.[1] With appropriate treatment, however, affected patients can achieve sustained remission.[2] This disorder may involve the use of illicit opioids, as well as prescription opioid medication used non-medically.[2]

In recent years, the number of overdose deaths associated with opioids in Canada has increased at an alarming rate. In 2016, a total of 967 illicit drug overdose deaths were recorded in British Columbia, almost a 50% increase from 2015.[3] Alberta saw an elevation in overdose deaths in 2016 with 343 fentanyl-related deaths, a 25% increase from 2015.[4] In the first five months of 2017, British Columbia has reported 640 overdose deaths.[3] Front-line responders in Canada have signaled that this crisis is also moving eastward.[4] Although all casualties may not meet criteria for OUD, health care providers have identified a need to increase access to addiction care and treatment for high-risk opioid users in order to reduce overdose deaths, and react to posed threats to public safety.[2]

The goals of OUD treatment are multifaceted, and include harm reduction, abstinence from or reduction in illicit opioid use, and reduction in criminal activity.[4] Pharmacological therapy, such as opioid agonists, are a cornerstone of this treatment, for its ability to suppress craving and withdrawal symptoms, and block the acute effects of other opioids.[5] Opioid agonist therapy can function as a tool to reduce opioid use and its adverse effects.[6] Two opioid agonists prescribed for this purpose in Canada are methadone and buprenorphine.

For many years, methadone has been the most commonly prescribed opioid agonist for OUD in Canada.[2] However, recent reports have highlighted a low number of methadone prescribers per capita in Canada, particularly in Northern regions, as well as poor compliance rates.[7] Safety also remains an ongoing concern, as a recent BC review of prescription opioid-related deaths found methadone to be involved in approximately 25% of overdose fatalities.[8] Although data for buprenorphine-related harms are limited, some cohort studies indicate buprenorphine to be a safer option for treating OUD, specifically with regard to overdose risk.[8-10] In light of this, there is a growing interest to explore the option of using buprenorphine formulations more routinely as a first-line option for OUD.[1,11]

Currently, buprenorphine formulations for the treatment of OUD include an implant, as well as oral formulations combined with an opioid antagonist, naloxone.[12] This combination is designed to discourage abuse of buprenorphine, as naloxone can precipitate withdrawal symptoms in patients with OUD.[12] Buprenorphine-naloxone combination formulations include a sublingual tablet, sublingual film, and high-bioavailability sublingual tablet. Only the sublingual tablet formulation of the buprenorphine-naloxone combination (Suboxone) is licensed for use in Canada.[12] On 21 April 2017, Health Canada proposed to allow the importation and use of medications that have been authorized for sale in the United States, European Union or Switzerland, but are not yet authorized in Canada.[13] Once this process is implemented, this medication list could potentially include newer buprenorphine formulations available in the US.[14] The purpose of this report is to evaluate the clinical effectiveness, cost-effectiveness and evidence-based guidelines for the use of newer and unique buprenorphine formulations in patients with OUD.

Research Question

1. What is the comparative clinical effectiveness of various buprenorphine or buprenorphine-naloxone formulations for the treatment of opioid use disorders?
2. What is the cost-effectiveness of various buprenorphine or buprenorphine-naloxone formulations for the treatment of opioid use disorders?
3. What are the evidence-based guidelines regarding the use of various buprenorphine or buprenorphine-naloxone formulations for the treatment of opioid use disorders?

Key Findings

There is a paucity of high quality, large-scale randomized controlled trials comparing clinically relevant outcomes of effectiveness between different buprenorphine formulations for the treatment of opioid use disorder. Results were assessed in five randomized controlled trials and three non-randomized studies. No systematic reviews comparing the various buprenorphine formulations were found. All the buprenorphine formulations examined in the selected studies showed a similar clinical response in patients with opioid use disorder, with significantly higher rates of abuse, misuse and diversion found in sublingual buprenorphine-naloxone tablet formulations. The use of buprenorphine implants was associated with high rates of treatment retention. The rates of adverse effects were low among buprenorphine formulations with no significant differences observed. Within the clinical studies which met inclusion criteria, all but two were industry-sponsored and there were limitations with respect to study design, clinically relevant outcomes and treatment duration.

There was one economic evaluation which demonstrated cost-effectiveness of the use of buprenorphine implants over sublingual buprenorphine-naloxone film, with respect to clinical outcomes and lower costs from a societal perspective. However, results from this study should be interpreted with caution due to limitations in this study.

There are no Canadian or American clinical practice guidelines identified which specifically compare and evaluate different formulations of buprenorphine for OUD. One Australian guideline was found which suggested the use of buprenorphine-naloxone sublingual film over tablets due to ease of supervision and potential decreased risk of diversion.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, TRIP database, University of York Centre for Reviews and Dissemination (CRD), Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized trials, guidelines and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2012 and June 29, 2017.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with opioid use disorders
Intervention	Various formulations of buprenorphine or buprenorphine/naloxone (ie. Sublingual films/tablets, implants, IM depot)
Comparator	Q1-2: Various formulations of buprenorphine or buprenorphine/naloxone (ie. Sublingual tablets/films, implants, IM depot) Q3: No comparator
Outcomes	Q1: Clinical effectiveness (e.g., reduction in opioid consumption, prevention of relapse, maintenance of abstinence, retention into treatment, adherence to medications, social functioning [e.g., return to school or work], emotional and psychological functioning [e.g., anxiety, depression, sleep]); Safety (e.g., misuse and diversion, reports or evidence of abuse, urine drug screening results) Q2: Cost-effectiveness outcomes (e.g., ICER, QALY) Q3: Evidence-based guidelines on the use of different buprenorphine formulations
Study Designs	Health technology assessments, systematic reviews and meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, guidelines

ICER= incremental cost-effectiveness ratio; IM = intramuscular; QALY=quality-adjusted life year.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2012. Economic evaluations that did not conduct a cost-effectiveness or cost-utility analysis were excluded. Guidelines that did not provide a description of their methodology, and those lacking a formal literature search or system to evaluate the strength of the evidence and recommendations were also excluded.

Critical Appraisal of Individual Studies

The included randomized controlled trials and non-randomized studies were critically appraised using the Downs and Black checklist,[15] economic studies were assessed using the Drummond checklist,[16] and guidelines were assessed with the AGREE II instrument.[16] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 518 citations were identified in the literature search. Following screening of titles and abstracts, 468 citations were excluded and 50 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 43

publications were excluded for various reasons, while ten publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Five randomized controlled trials (RCTs),[17-21] two non-randomized studies,[22,23] and one economic evaluation[24] met the inclusion criteria. A preliminary publication[19] was available for one included randomized controlled trial, Gunderson 2016,[25] which was released before the study's completion. The results of this preliminary study were covered in the final publication.[25]

Two of the RCTs were double-blind, non-inferiority, double-dummy, active-controlled trials,[17,20] one was a double-blind, placebo-controlled trial with an open-label active-controlled component,[18] and two of the RCTs were open-label for the maintenance phase of the study.[21,25] One of the open-label RCTs included an induction phase for the first three days which was randomized and double-blinded, as well as a cross-over after the maintenance phase.[25] The second open-label RCT had an induction phase for the first three days which was randomized and blinded to the patient and the sponsor.[21]

The three non-randomized studies[22,23,26] were observational, retrospective cohort analyses that evaluated electronic databases.

One economic evaluation was a cost-effectiveness analysis using a Markov model with a time horizon of 12 months which was conducted from a US societal perspective.[24] It involved movement between four mutually-exclusive health states: on treatment, not relapsed; on treatment, relapsed; off-treatment, relapsed; and dead.

One clinical practice guideline[27] met the selection criteria (Appendix 2, Table A3). This guideline was developed in 2014 by the Commonwealth Department of Health and commissioned by the Intergovernmental Committee on Drugs in Australia.[27] The development of this guideline correlated with national and international research. The first stage involved identifying issues and needs to be addressed, based on previous guidelines and experience by the authors involved. Literature searches were subsequently undertaken to identify recent systematic reviews and clinical trials (published after 2000) of pharmacotherapies based on the outlined issues. A grading system was devised in order to assess the evidence statements made.

Country of Origin

One RCT was conducted within multiple sites in Australia[17] and the other four RCTs[18,20,21,25] and economic evaluation[24] were conducted within multiple sites in the USA. All three non-randomized studies[22,23] were conducted within databases containing a USA population.[22,23] The included guideline was based in Australia.[27]

Patient Population

The number of recruited patients in included RCTs ranged from 92 patients to 758 patients. The diagnosis of OUD was confirmed based on the Diagnostic Statistical Manual of Mental Disorders (DSM) criteria in all RCTs.[17,18,20,21,25] Two of these RCTs were conducted in patients who had not received methadone or buprenorphine in 90 days prior to enrollment[18,21] and one RCT[25] included patients with mild withdrawal symptoms and one negative urine drug screening prior to admission. The final two RCTs[17,20] were conducted in patients already on continuous buprenorphine treatment; in one study patients were on treatment for at least three months with a stable dose for at least 30 days,[17] in the other study, patients had a history of continuous buprenorphine treatment for at least 24 weeks.[20]

The three non-randomized trials included patients who had evidence of being administered buprenorphine-naloxone film or tablets. One non-randomized study evaluated electronic medical records for patients admitted to 34 treatment facilities across the USA,[23] and the other non-randomized trial used a private USA insurance claims database that represented over 30 million insured individuals from several large health insurance plans in the country.[22] The third non-randomized trial[22] included information from the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) which evaluates trends in opioid misuse, abuse and diversion through the utilization of US Poison Center, Drug Diversion Program, and treatment program data. All three sources of data were included in their analysis based on the number of persons filling opioid prescriptions. The number of recruited patients in these studies ranged from 3,233 to 12,351 patients.

The one economic evaluation[24] included in this analysis was populated by outcomes from one included non-inferiority RCT[18] which included 287 patients with OUD who had not received buprenorphine-naloxone in the 90 days prior to enrollment. This RCT populated data for the movement between the states of being on treatment and not relapsed to being on treatment and relapsed. The remaining transitions (moving from relapsed, on treatment to relapsed, off treatment; and relapsed, on treatment to dead) were modeled with inputs drawn from selected peer-reviewed literature. The rationale provided for this was that these health-state models are not represented in clinical trials, and that peer-reviewed literature would provide more real-world data. The proportion of the cohort relapsing was based on the proportion of patients in the RCT who reported being primary users of heroin. The proportion of patients at risk of intravenous misuse and accidental pediatric poisoning with buprenorphine were only measured in those patients who were documented to have been prescribed sublingual buprenorphine-naloxone throughout the RCT (also included proportion of patients in the buprenorphine implant arm who had received supplemental doses of sublingual buprenorphine-naloxone). Costs associated with clinical and societal consequences of relapse were drawn from observational studies and administrative claims analyses, which were identified through a targeted review of peer-reviewed literature. They were then adjusted to 2016 USD using a recent version of the Consumer Price Index for all urban consumers from the United States Bureau of Labor Statistics.

The one included guideline[27] aims to provide context and understanding to the selection and options for management of opioid dependence therapy available in Australia. The intended users of this guideline were identified to be clinicians working with in both general and specialist settings.

Interventions and Comparators

In two of the RCTs,[21,25] patients were randomized to receive either intervention treatment, which was a high-bioavailability rapidly dissolving buprenorphine-naloxone fixed-dose sublingual tablet (Zubsolv, 5.7 mg or 1.4 mg of buprenorphine), or comparator treatment, which was generic buprenorphine for the induction phase (8 mg or 2 mg), defined as the first two days of enrollment. In the subsequent maintenance phase of the study (day 3 onwards), patients in the comparator arm were switched to buprenorphine-naloxone film (Suboxone, 8 mg or 2 mg of buprenorphine). The treatment duration in one of these RCTs[25] was 22 days, and 29 days in the second RCT,[21] with the two-day induction phase included.

One RCT[17] and two non-randomized studies[22,26] compared two formulations of sublingual buprenorphine-naloxone, the intervention being the buprenorphine-naloxone film (8 mg or 2 mg of buprenorphine, Suboxone film) and control being the buprenorphine-naloxone tablet (8 or 2 of buprenorphine, Suboxone tablet). The treatment duration in the RCT[17] was 31 days. One non-randomized study[22] obtained data for approximately 56 months before and 27 months after the film formulation of buprenorphine-naloxone was approved in the USA in 2010 (from Jan 1 2006 to November 30, 2012). The second non-randomized study[26] obtained data for a 27 month period from 1 October 2010 to 31 December 2012, also after the film formulation of buprenorphine-naloxone was approved in the USA.

In two of the RCTs[18,20] the intervention was four buprenorphine implants (BI) (Probuphine, 80 mg each). One of these RCTs[18] used four placebo implants as a comparator, as well as open-label sublingual buprenorphine-naloxone (12 to 16 mg of buprenorphine once daily) available to all included patients. There was a third arm of the study that included patients on open-label sublingual buprenorphine-naloxone (12 to 16 mg of buprenorphine once daily). In both of these studies, either the active or placebo implant was both inserted and removed at six months in a 10 to15 minute in-office procedure. One study[20] specified that this was carried out by staff which were not involved in the study evaluation in an attempt to preserve blinding, as there was a slightly varied appearance between active and placebo implants. The other study[18] stated that the implanting clinician was the only unblinded member of staff involved in the study. The treatment duration was 24 weeks. The second RCT[20] used four placebo implants as a comparator, as well as generic buprenorphine tablets (dosage as pre-randomization) available to all patients. The treatment duration in this study was 26 weeks. Since the economic evaluation[24] was modeled on this RCT, the same intervention (buprenorphine implants, Probuphine, 80 mg each) and comparator (sublingual buprenorphine) were applied.

One of the non-randomized studies[23], compared buprenorphine (Subutex, other generics) to sublingual buprenorphine-naloxone (Suboxone) as well as methadone in a separate arm.

The interventions set out to be assessed by the included guideline[27] were current first-line options in the management of OUD in Australia. These interventions specifically included methadone, buprenorphine and naltrexone.

Outcomes

The main outcomes reported in the RCTs included:

- Proportion of negative urine opioid screenings[17,18,20]
- Self-reported substance use (opiate,[17,18,20] amphetamines,[17] cannabis,[17] benzodiazepines,[17] alcohol[17])
- Retention into treatment[18,21,25]

- Adverse effects[17,18,20,21,25]
- Opiate Withdrawal Scales (Clinician (COWS)[18,20,21,25], Subjective (SOWS([17,18,20,21,25], Objective (OOWS)[17])
- Visual analog scales (for cravings,[17,18,20,21,25] and sedation[18])

In one included RCT,[20] the primary outcome was defined as patients with at least 4 to 6 months with no evidence of illicit opioid use. This was a composite of cumulative negative opioid urine samples and self-reported opioid abstinence obtained together at scheduled monthly visits and four times randomly for a total of 10 urine samples.

The outcomes in one of the non-randomized studies[22] were time to discontinuation of buprenorphine-naloxone, treatment retention rates, and resource utilization (such as pharmacy claims, probability of hospitalization, and outpatient visits). The mean number of pharmacy claims and outpatient visits during the 12-month period before and after buprenorphine-naloxone treatment was compared.

The outcomes in the second non-randomized study[23] were positive urine samples for opioids, treatment retention and length of stay in treatment.

The outcomes in the third non-randomized study,[26] were total number of reports and rates of intentional abuse, diversion, and abuse by non-oral routes documented by the Poison Center and Drug Diversion Program. Outcomes also included self-reported incidences of abuse and misuse by participants of treatment programs.

The outcomes in the economic evaluation[24] were incremental cost per quality-adjusted-life-year (QALY) gained and incremental net-monetary-benefit (INMB).

Outcomes evaluated in the included guideline[27] were a combination of safety and effectiveness. Safety outcomes included side effect profile, drug interactions, sedation, and overdose risk. Effectiveness outcomes emphasized abstinence rates, retention into treatment, and social functioning.

Summary of Critical Appraisal

The strengths and limitations of the included reports are summarized in Appendix 3.

In regard to included clinical studies, objectives and selection criteria were stated in all. Patient characteristics, interventions and outcomes were well described in six of the clinical studies.[18,20-23,25] Intervention and outcomes were well-described in one of the studies, whereas patient characteristics were described in a limited capacity.[17] Four of the included RCTs had computer-generated randomizations with double-blinded allocation.[17,18,20,25] One of these studies had computer-generated randomization; however, allocation was blinded to the patient and sponsor but not the outcome assessor, which may be a source of ascertainment bias in the study.[21] In two of the included RCTs, only the induction phase (days 1-2) were double-blinded[25] or blinded to patient and sponsor,[21] however the maintenance phase (day 3-onwards) was open-label, which can leave these studies vulnerable to ascertainment bias.[21,25] Intention-to-treat (ITT) analyses were performed in all RCTs with the exception of one study,[25] where the primary outcome was conducted in a per-protocol population, which may exaggerate the estimate of treatment effect. However, for this study a sensitivity analysis was conducted on data for the entire study cohort, which was consistent with these findings. All included studies were industry sponsored, with the exception of one retrospective cohort study.[23] All RCTs provided a power calculation for which their choice of sample size was based on. Two included clinical studies[23,26] would

have results that would be generalizable to real-world patients with OUD because one study[23] included all records for patients at 34 treatment facilities attending a treatment program with both methadone or buprenorphine, and another study[26] included all reports collected from US poison center control, drug diversion and treatment programs. This contrasts with some included RCTs with selection criteria which often excluded patients previously treated with buprenorphine-naloxone,[18,21] patients with AIDS,[18,20] or patients not meeting compliance criteria.[17,23] In regard to study duration for included RCTs, treatment duration and follow-up ranged from 22 days to 26 weeks, which is unlikely to be a sufficient length of time to assess whether abstinence or use reduction can be maintained in this patient population.

In the economic evaluation, the research questions, purpose of study and specified viewpoint (societal perspective) was clearly described. The resource utilization and costs included in the study were described and justified. Univariate and probabilistic sensitivity analyses were conducted using minimum and maximum acceptable values for inputs, which reflected results of peer-reviewed literature in a targeted review. In regards to limitations of this study, the design was modelling a 12 month time horizon by utilizing an exponential function on an RCT[20] that was 24 weeks in duration, and it is uncertain that 24 week clinical outcomes would hold at one year. Furthermore, many of the societal outcomes (i.e., criminal justice involvement, lost wages, emergency department visit and hospitalization rates) explored in this analysis were not recorded in the primary study, therefore it was assumed that the probabilities of arrests and relapse-related healthcare utilization was increased among study subjects who discontinued treatment. Another outcome, relapsing to intravenous heroin (as opposed to oral prescription opioids) was based on the proportion of patients in the referenced RCT[20] who reported being primary users of heroin. The proportion of primary heroin users in this study was a description only measured at baseline for this RCT; therefore, any results of this outcome in an economic analysis would bear no correlation to the intervention used. Also, this study was fully industry-sponsored, and based on USA costing information, which may limit its generalizability in a Canadian health care system.

The included guideline was developed by a professional association with contribution by an expert committee based on a systematic review process that was well described.[27] The objectives, clinical questions and population for whom the guidance was intended were well described. Guideline development groups were representative of their professional groups and recommendations were peer-reviewed by relevant bodies. Recommendations were presented clearly and linked to supporting when relevant. Conflict of interest was not elaborated on in the guidance and an update plan was not provided.[27]

Summary of Findings

The overall findings are summarized below and detailed findings from the individual studies are provided in Appendix 4.

What is the comparative clinical effectiveness of buprenorphine formulations for the treatment of patients with opioid use disorder?

Buprenorphine Implants vs. Placebo + sublingual buprenorphine-naloxone

Two RCTs[18,20] evaluated non-inferiority of BI to placebo implants (PI) with sublingual buprenorphine-naloxone. In one study,[20] the proportion of opioid-negative urine samples was only presented in combination with self-reports of opioid use. It was found that the

composite of cumulative negative opioid urine samples and self-reported opioid abstinence at 6 months was significantly higher in the BI group compared to PI + sublingual buprenorphine-naloxone (85.7% in BI group vs. 71.9% in PI + sublingual buprenorphine-naloxone group, p=0.03, 95%CI 0.018 to 0.258). Similarly in the second study,[18] there was a significantly higher mean of cumulative 6 months opioid-negative urine samples observed in the BI group (36.0% n BI group vs. 14.4% in PI + sublingual buprenorphine-naloxone group, p<0.0001). However in this study it is worth noting that the drop-out rate in the placebo group was exceptionally high (74.1%), and by design of the study, when a subject was discontinued or withdrawn from the study, urine samples from that point onward were considered positive. It is unlikely that all patients who were discontinued or withdrawn from the study in the placebo arm would have yielded a positive urine sample; therefore, these results should be interpreted with caution. In the BI group of both studies,[18,20] supplementary medication with sublingual buprenorphine was required, which was able to be prescribed by an investigator for symptoms of opiate withdrawal and cravings: 17.9% (15/84) and 39% (45/114) respectively. In regard to other clinical outcomes, there were no significant differences observed between groups in subjective, standardized scales of opioid cravings, sedation and withdrawal symptoms performed by self-reporting and clinicians. In regard to adverse events, one study[18] did not find any significant differences in adverse events between groups, and the second study[20] reported all adverse events, although it was not powered to detect any differences.

Buprenorphine-naloxone sublingual film vs. buprenorphine-naloxone sublingual tablet

One RCT[17] compared sublingual film and tablets and found there to be no significant differences between groups when evaluating clinical effectiveness. Parameters included treatment retention, self-reported abstinence confirmed by urine drug screenings, patient preference, self-reported cravings, withdrawal and sedation, global measures of well-being and self-reported substance use. In regards to safety outcomes in this study, there was a significantly longer mean dissolution time observed in tablet (242 ± 141s) than film (173 ± 71s) groups (p=0.007, F=7.668) during the open-label phase of the study. There is an implication that a shorter dissolution time can reduce risk of diversion and decrease time required to supervise dosing (although these outcomes were not directly measured). There was also a signal that the sublingual film would be difficult to remove wholly or partially at 30s and 60s after dosing, which may further contribute to abuse-deterrence with the use of this formulation. No significant differences between groups with respect to the number of side effects were reported.

One retrospective non-randomized study[22] evaluated outcomes of the use of sublingual film and tablets in previously untreated patients with OUD in the context of persistence rates. Between the two formulations, there were 1,134 cases of discontinuation in the film group vs 821 in the group taking tablets. However, the time to discontinuation was significantly longer in the film group after adjustment of covariates (ie. age, geographic area, type of health insurance plan) (HR 0.818, p=0.0005). Treatment retention at 6 months was also found to be higher in the film group at 63.78% vs 58.13 in the tablet group (p=0.02). This study also reported that mean numbers of pharmacy claims and the probability to have an emergency room visit were not significantly different between the formulations. It was found that there was a higher number of outpatient visits in the film group after starting treatment vs the tablet group (9.88 vs 9.51, p=0.0185), however there was a higher probability to have at least one hospitalization in the tablet group compared to film (0.23 vs 0.19, p=0.0158). Although logistic regression was applied, this result should be interpreted

carefully as there was a higher probability of hospitalization in this group before enrollment between groups (0.34 vs 0.3, p=0.004).

Another retrospective non-randomized study[26] found there to be much higher rates of both abuse and diversion in sublingual tablets compared to sublingual film. It was found that the average abuse rate with tablets was approximately four times that of film preparations, there were 11 times as many drug diversion cases involving tablets than in film and in treatment programs, the abuse rate of tablets was twice that of films. Rates of abuse via both parenteral and nasal routes, and injection routes only were reported to be higher for tablet formulations than for film formulations.

Buprenorphine-naloxone high-bioavailability sublingual tablet vs generic buprenorphine

Two RCTs[21,25] examined non-inferiority of high-bioavailability sublingual tablets (BN-HBT) to generic mono buprenorphine sublingual tablets (BUP). Both studies had a randomized, blinded two day induction period, followed by an extended open-label maintenance phase. One study ended with a cross-over phase.[25] Treatment retention for this study[25] was measured at day 3 (after induction phase), day 15 (after maintenance phase) and day 22 (after cross-over phase). In the second study,[21] treatment retention was reported only at day 3 (after induction phase). Both studies included per protocol and ITT analysis for this outcome. In the first study,[25] treatment retention within the entire cohort within the end was similar between groups for day 3 (93.2% in BN-HBT vs. 91.7% in BUP, p=0.440), day 15 (74.9% in BN-HBT vs. 74.4% in BUP, p=0.866) and day 22 (68.4% in BN-HBT vs 69.9% in BUP, p=NS). Alternatively, in the second non-inferiority study,[21] there was a significantly higher treatment retention seen in the generic buprenorphine group (88.3% in BN-HBT vs. 95.3% in BUP, p=0.040; 95%CI: -13.7 to -0.4) when analyzing the per-protocol sample. In this study, BN-HBT was did not meet non-inferiority criteria when compared to generic buprenorphine. Opioid withdrawal symptoms were also measured in these studies,[21,25] where no significant differences were noted in subjective, standardized scales for withdrawal, cravings, and sedation conducted via clinician and self-reporting. When examining safety outcomes, there were no significant differences noted between groups in both studies when evaluating adverse effects.

What is the cost-effectiveness of different buprenorphine formulations for the treatment of patients with opioid dependence?

One economic evaluation[24] compared the cost-effectiveness of using buprenorphine implants to a sublingual buprenorphine-naloxone formulation from a societal perspective, and found that buprenorphine implants were found to be more cost-effective, in an 88% probability across the 1,000 bootstrapped simulations at $50,000 per QALY. There was also a favourable INMB at a willingness-to-pay threshold of $50,000. This cost-benefit was favourable despite higher drug acquisition costs ($9,414 vs. $2,922) and supplemental use of sublingual buprenorphine-naloxone ($54 vs. $37). These outcomes, however, seem to have been driven by a decrease in emergency room and hospitalization costs ($8,444 in BI group vs $16,484 in sublingual buprenorphine-naloxone group) as well as criminal justice costs ($1,265 in BI group vs $3,088 in sublingual buprenorphine-naloxone). These results should be interpreted with caution, as it was derived from treatment discontinuation rates within a clinical trial[20] from a 24-week study extrapolated using an exponential function.

What are the evidence-based guidelines regarding the use of different buprenorphine formulations for the treatment of patients with opioid use dependence?

One national guideline from Australia compares sublingual tablet and film preparations of buprenorphine-naloxone. This guideline suggests the use of sublingual film preparations, due to its ease in the supervision of its administration, as well as a potential reduction in diversion. The rationale for this recommendation is based on results from one of the included RCTs.[17] While this guideline did provide evidence gradings within its report, there were none reported for the statements relevant to buprenorphine formulations.

No guidelines which originate from the USA or Canada were found which draw comparisons between different formulations of buprenorphine used in opioid use disorder.

Limitations

Patients in the included RCTs received treatment for 26 weeks or less, which may not be long enough to fully measure the effectiveness of these interventions for this complex condition.

All of the RCTs which met selection criteria were industry sponsored. Furthermore, two of the included RCTs[21,25] had a randomized, blinded induction phase which lasted two days, and after which was open-label. One of these studies[21] was double-blinded for the induction phase, and the other RCT[25] was blinded only to the patient and sponsor, which could introduce ascertainment bias on the part of the assessor.

Two RCTs[21,25] included generic oral buprenorphine as a comparator, which is no longer the standard of care as an abuse deterrent strategy.[27] Oral buprenorphine-naloxone is less likely to be injected than mono preparations containing only buprenorphine.[27]

All of the included RCTs comparing buprenorphine implants to oral formulation[18,20] allowed for rescue medication with oral medication if needed, making it difficult to compare outcomes.

Many of the clinical studies used self-reporting and subjective scales to assess abstinence from opioid or heroin use, which may lead to under-reporting. This is also problematic from a study design perspective as study participants may feel pressured to not provide answers that would compromise their place in a treatment program. Analyzing urine samples would be a more objective method for determining effectiveness, which was documented to have been conducted in three of the five RCTs.

One US observational study[26] which measured rates of abuse and diversion between buprenorphine-naloxone sublingual film and tablet formulations collected data over a 27 month period right after film formulations were introduced onto the US market. This may not an adequate amount of time to measure this outcome, especially since diversion rates in film preparations may have been subject to increase as it becomes more established.

No systematic reviews were identified which specifically compared the use of these formulations. One guideline from Australia discussed a preference of buprenorphine-naloxone sublingual film over tablets, however this statement was not graded.[27]

None of the included studies or economic evaluations were conducted in Canada, thus applicability of the findings in a Canadian setting is unclear.

Conclusions and Implications for Decision or Policy Making

All the buprenorphine formulations examined in the selected studies showed a similar clinical response in patients with opioid use disorder, with significantly higher rates of abuse, misuse and diversion found in sublingual buprenorphine-naloxone tablet formulations.

The use of buprenorphine implants was associated with high rates of treatment retention. The rates of adverse effects were low among buprenorphine formulations with no significant differences observed. Observational retrospective data has found sublingual combination film formulations to carry low rates of abuse and diversion. The findings indicate that the use of newer available buprenorphine formulations may be safe to use in this population, but the included trials were relatively short in duration and may have been underpowered to detect rarer adverse effects. Larger studies with longer treatment durations are required to better understand the safety profiles of these newer formulations.

Conclusions on the best practices regarding the use of buprenorphine formulations for patients with opioid use disorder cannot be drawn while no relevant systematic reviews or evidence-based guidelines which consider all available evidence were identified.

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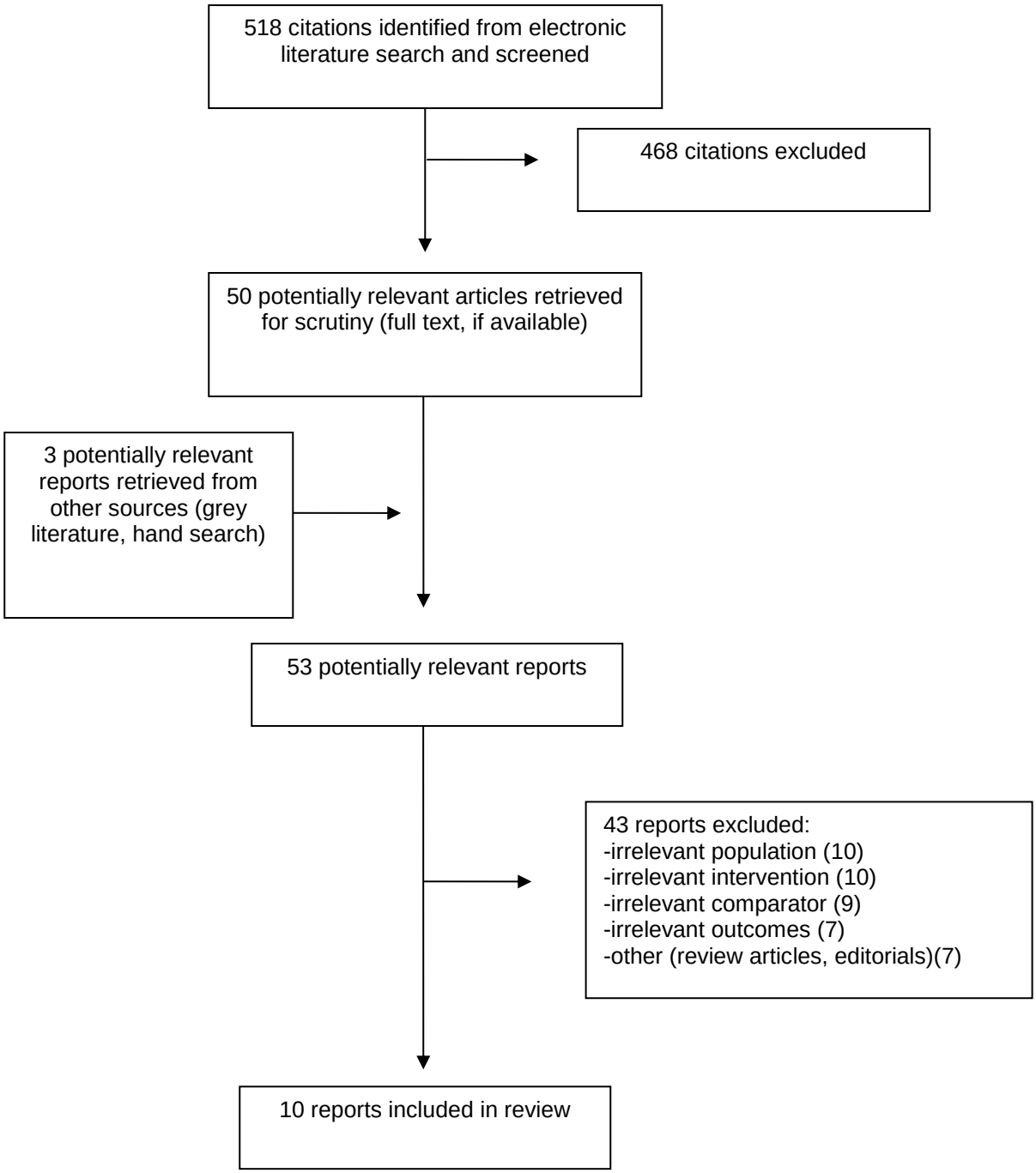
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Study Sample Size	Intervention(s)	Comparator(s)	Main Clinical Outcomes
RCTs					
Lintzeris, 2013[17] **Australia**	Double-blind, active-controlled double-dummy RCT 31 days (Day 1-7 open-label, Day 8-17 randomized double-blind, double-dummy, Day 18-31 open-label) ITT analysis	Adult patients with OUD in continuous buprenorphine treatment ≥3 months, on stable dose ≥30 days N=92	BN-F Supervised daily dosing: Day 1-17; Pre-trial dosing conditions: Day 18-31 N=44 (n=12 low dose, n=32 high dose)	BN-T Supervised daily dosing: Day 1-17; Pre-trial dosing conditions: Day 18-31 N=48 (n=18 low dose, n=30 high dose)	OOWS, SOWS, VAS for sedation, craving, dissolution time; AE; Self-reported substance use; proportion of negative urine drug screenings between groups; WHOQOL-BREF
Rosenthal, 2013[18] **USA**	Double-blind, placebo-controlled RCT; open-label, non-inferiority trial 24 weeks (excluding open-label induction phase with target 12-16mg/day for 3 consecutive days) ITT analysis	Adult patients OUD who had not received methadone or buprenorphine for opioid dependence within 90 days N=287	BI N=114	Placebo implant (PI) N=54 BN-SLT (open-label, non-inferiority; margin 15%) N=119	Mean CDF of percentage urine opioid-negative screenings; self-reported opioid use; retention in treatment at 24 weeks; percentage of negative urine opioid readings week 1-16 and 17-24; SOWS; COWS, VAS for cravings; AE
Gunderson, 2016[25] **USA**	Open-label, parallel-group, non-inferiority RCT 22 days (2-day double-blinded induction; cross-over at day 15) ITT analysis on efficacy and safety measures only	Adult patients with OUD with at least mild withdrawal symptoms and a negative urine drug screen N=758	BN-HBT N=383	Generic BUP (induction, day 1-2); BN-F (maintenance, day3-onwards) N=375	Retention in treatment on days 3, 15 and 22; COWS, SOWS, VAS for cravings; AE
Rosenthal, 2016[20] **USA**	Double-blind, active-controlled, double-dummy RCT	Adult patients with OUD receiving sublingual buprenorphine	Four 80mg BI plus sublingual placebo tablets	Four placebo implants plus generic BUP	Opioid-negative urine test and self-reported opioid use; cumulative

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Study Sample Size	Intervention(s)	Comparator(s)	Main Clinical Outcomes
	26 weeks ITT analysis	treatment at least 24 weeks at ≤8mg N=177	N=87	N=90	percentage of opioid-negative urine test; VAS for cravings, AE; SOWS; COWS
Webster, 2016[21] **USA**	Open-label, active-controlled, non-inferiority RCT 29 days (2 day single-blinded induction phase, then open-label maintenance phase) Per-protocol analysis	Adult patients with OUD who have not received buprenorphine or naloxone within 90 days prior to start N=310	BN-HBT N=155	Generic BUP (induction, day 1-2); BN-F (day 3-onwards) N=155	Retention in treatment at day 3, COWS, SOWS, VAS for cravings, AE
Non-RCTs					
Clay, 2014[22] **USA**	Retrospective, cohort analysis using electronic database	Patients with evidence of buprenorphine-naloxone sublingual tablets/film treatment from 01 January 2006 to 30 November 2012 N=4,306	BN-F N=2,796	BN-T N=1,510	Time to discontinuation, persistence rates, switch rates, average daily doses, resource utilization such as pharmacy and outpatient claims, probability of hospitalization, related healthcare costs
Proctor, 2014[23] **USA**	Naturalistic comparison of methadone, buprenorphine-naloxone sublingual tablets and buprenorphine-naloxone sublingual films. Data abstracted from electronic medical records for 6 months or until discharge	Patients admitted to 34 maintenance treatment facilities with evidence of either methadone or buprenorphine-naloxone film/tablet treatment in the US from 01 July 2012 to 01 July 2013 N=3,233	BN-T N=102	BUP N=393 (Methadone also a comparator: N=2,738)	Positive urine samples for opioids, treatment retention, length of stay in treatment

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Study Sample Size	Intervention(s)	Comparator(s)	Main Clinical Outcomes
Lavonas, 2014[26] **USA**	Retrospective cohort analysis using electronic database; included data from online questionnaire	Unique patients filling prescriptions for sublingual buprenorphine formulations from 01 October 2010 and 31 December 2012 N=12,351	BN-T	BN-F	Number of patients filling prescriptions, number of reports of intentional abuse per 10,000 URDD, number of cases of buprenorphine diversion per 10,000 URDD, reports of abuse by non-oral routes per 10,000 URDD

AE= adverse events; BI= buprenorphine implant; BN-F= buprenorphine-naloxone sublingual film; BN-HBT= buprenorphine-naloxone high-bioavailability sublingual tablet BN-T= buprenorphine-naloxone sublingual tablet; BUP= sublingual buprenorphine (generic); COWS= Clinician Reports of Withdrawal Symptoms; CDF= cumulative distribution functions; ITT=I intention-to-treat; OOWS= Objective Opioid Withdrawal Scale; OUD= opioid use disorder; RCT= randomized controlled trial; SOWS= Subjective Opioid Withdrawal Scale; WHOQOL-BREF= World Health Organization Quality of Life Brief; URDD= unique recipients of dispensed drug; USA= United States of America; VAS= visual analog scale.

Table A2: Characteristics of Included Cost Studies

First auther, Publication Year, Country	Type of Analysis, Perspective	Intervention, Comparator	Study Population	Time Horizon	Main Assumptions
Carter, 2017[24] **USA**	Cost-effectiveness analysis Societal perspective Probabilities were derived from RCT[20] and extrapolated to 12 months with an exponential function; remaining transitions modeled with inputs drawn from peer-reviewed literature	BI, generic BN	Opioid-dependent patients included in RCT[20]	12 months	- Only considered clinically stabilized patients (≤8mg/d) - Results observed at in trial conditions at 24 weeks would be the same as at 12 months in real-world conditions

BI= Buprenorphine implant; BN= Sublingual buprenorphine-naloxone; HR= hazard ratio; RCT= randomized controlled trial.

Table A3: Characteristics of Included Guidelines

Objectives			Methodology		
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, selection and synthesis**	**Recommendations development and Evaluation**	**Guideline validation**
Australia National Guidelines for Medication-Assisted Treatment of Opioid Dependence, Gowing, 2014[27]					
Users: Physicians, pharmacists, policy-makers Targets: adults and adolescents with opioid dependence in Australia	Treatment approaches that combine medication and psychosocial support for opioid dependent patients	Efficacy, safety, tolerability and feasibility	Literature searches for recent (published since 2000) systematic reviews and clinical trials of pharmacotherapies	Specific wording of guidelines and supporting information collated, and grading system allocated based on the Commonwealth Department of Health	Reviewed by the Commonwealth Department of Health and the Intergovernmental Committee on Drugs

Appendix 3: Critical Appraisal of Included Publications

Table A4: Strengths and Limitations of Randomized Controlled Trials using Downs and Black Checklist[15]

Strengths	Limitations
RCTs	
Lintzeris, 2013[17]	
- Objectives and inclusion/exclusion criteria were stated. - Interventions and outcomes were described. - Double-blind, double-dummy randomized study. Computerized random numbers were used for the randomization procedure. Treatment assignments were placed in sealed, opaque envelopes. - ITT analysis performed on primary analysis. - Choice of sample size was justified. - Number of patients discontinued or lost to follow-up were reported.	- Patient characteristics were described in a very limited way (only mean patient age provided) - Generalizability limited: uncertain as to whether study patients were representative of all patients (limited patient characteristics provided, did not include patients who missed >2 doses per week), - Industry provided both study medications and sponsored study - Clinically relevant outcomes were self-reported, with the exception of urine drug screenings. - Results not fully provided. Did not report numerical results for urine drug screening, p-values, dissolution time and adverse events in randomized phase. - Dissolution time and ability to remove film are not clinical outcomes, but may reduce diversion, reduce length of supervision time. - Length of treatment and follow-up: 1 month.
Rosenthal, 2013[18]	
- Objectives and inclusion/exclusion criteria were stated. - Patient characteristics, interventions and outcomes were described. - Double-blind, placebo-controlled randomized trial. Computerized generator used for randomization procedure with blinded allocation. - Statistical testing done, and fixed sequence testing procedure applied to minimize Type I error risk. Adjustments made for covariates were clearly listed. - ITT analysis performed on primary analysis. All missed urine samples, withdrawals and discontinuations were considered urine sample-positive. - Choice of sample size was justified. - Number of patients discontinued or lost to follow-up were reported.	- Industry-funded study; many authors received additional funding from manufacturer - High drop-out rate in placebo arm of trial (74.1%); as all withdrawals and discontinuations considered urine sample-positive there is potential to skew results toward rejection of null hypothesis - Comparison of buprenorphine implant to sublingual tablet was unblinded. - Generalizability limited: patients receiving methadone or buprenorphine for opioid dependence within 90 days were excluded from study - Rescue medication of sublingual buprenorphine-naloxone in all groups makes it difficult compare outcomes - Length of treatment and follow-up: 24 weeks
Gunderson, 2016[25]	
- Objectives and inclusion/exclusion criteria were stated. - Patient characteristics, interventions and outcomes were described. - 2-day double-blinded, active-controlled randomized induction, followed by open-label, active-controlled trial, with cross-over. - Computerized generator used for randomization procedure with double-blinded allocation for induction phase - Choice of sample size was justified. - Both ITT and per protocol analyses were provided	- Industry-funded study. - Clinically relevant outcomes were subjective scales, with the exception of retention of treatment. - Open-label during stabilization phase (Day 3-onward). - Patients were allowed rescue medication if needed, making it difficult to compare outcomes. - Length of treatment (including cross-over) and follow-up: 22 days.

Strengths	Limitations
- Number of patients discontinued or lost to follow-up were reported	
Rosenthal, 2016[20]	
- Objectives and inclusion/exclusion criteria were stated. - Patient characteristics, interventions and outcomes were described. - Double-blind, double-dummy, active-controlled RCT. - Centralized computer system used for randomization procedure with blinded allocation. Efforts were made to conserve blinding during insertion and removal of implants. - Statistical testing followed for non-inferiority study. - ITT analysis conducted on primary analysis. All missed urine tests imputed by randomly generated binary outcome (positive or negative for opioid use), with 20% penalty against active arm. - Choice of sample size was justified. - Number of patients discontinued or lost to follow-up were reported.	- Industry-funded study - Generalizability limited: only patients who showed no evidence of opioid withdrawal or illicit opioid-positive urine samples at least 90 days prior to study entry were included. Additionally, majority of patients were Caucasian with a high school education, and primary opioid of abuse was prescription pain relievers, thus uncertain as to whether study was representative of all patients - Sublingual buprenorphine used as comparator, not considered the standard of care - Compliance with sublingual buprenorphine/ sublingual placebo was measured via pill counts, but not reported - Supplemental medication of sublingual buprenorphine-naloxone in all groups makes it difficult compare outcomes - Length of treatment and follow-up: 24 weeks
Webster, 2016[21]	
- Objectives and inclusion/exclusion criteria were stated. - Patient characteristics, interventions and outcomes were described. - Statistical testing done. Adjustments made for covariates were clearly listed. - 2-day active-controlled randomized induction blinded to patient and sponsor, followed by open-label, active-controlled trial - Computerized generator used for randomization procedure with blinded allocation for induction phase - Modified ITT analysis (those who received at least one study dose) was applied to secondary outcomes - Choice of sample size was justified. - Number of patients discontinued or lost to follow-up were reported.	- Industry-sponsored study - Generalizability limited: only patients who showed no evidence of opioid withdrawal or illicit opioid-positive urine samples at least 90 days prior to study entry were included. - Open-label during maintenance phase (day 3-onward) - Primary efficacy assessment was retention into treatment measured early at day 3; non-inferiority measures were designed around this outcome - Clinically relevant outcomes were subjective scales; with the exception retention into treatment - Length of treatment and follow-up: 28 days
Non-RCTs	
Clay, 2014[22]	
- Objectives and inclusion/exclusion criteria were stated. - Patient characteristics, interventions and outcomes were described. - Statistical testing done. Adjustments made for covariates were clearly listed.	- Industry-sponsored study - Sampled population was accessed from a database of private health insurance holders, may not generalizable to all patients in USA with opioid use disorder - Patients in BN-F group were younger and had lower healthcare costs at baseline than BN-T group - Costs data were estimations using standard pricing algorithms applied to claims data rather than real costings - No attempt was documented to have been made at blinding assessors to opioid treatment. - Compliance/adherence to treatment not captured.

Strengths	Limitations
Proctor, 2014[23]	
- Objectives and inclusion/exclusion criteria were stated. - Patient characteristics, interventions and outcomes were described. - Statistical testing done. - Entire population was sampled; results may be generalizable.	- No attempt was made at blinding assessors to opioid treatment. - Compliance/adherence to treatment unknown.
Lavonas, 2014[26]	
- Objectives were stated, inclusion or exclusion criteria not described - Statistical testing done - Full US data from their poison center program, drug diversion program, full results of an online survey completed by college students; results may be generalizable - Not sponsored by industry	- Response bias applied to college student survey - Primary analysis contained 27 months of data in Poison Cente and Drug Diversion programs, 21 months of data in the treatment programs

BN-F=buprenorphine-naloxone sublingual film; BN-T= buprenorphine-naloxone sublingual tablet; ITT= intention-to-treat; RCT= randomized controlled trial.

Table A5: Strengths and Limitations of Economic Studies using Drummond[28]

Strengths	Limitations
Carter, 2017[24]	
- Clearly described purpose of study - Clearly described research questions and specified viewpoint (societal perspective) - Resource utilization and costs were described and justified - Sensitivity analyses, the range or distribution of values were clearly described - Provided detailed information on clinical inputs such as effectiveness	- Sponsored by manufacturer - Modeled time-horizon over 12 months based on extrapolating results from 24-week study using an exponential function; remaining transitions modeled on inputs drawn from peer-reviewed literature - Study was conducted using USD cost information from US societal perspective which may limit generalizability to Canada - Costs of BI implantation and explanation were estimated based on reimbursement amounts for subdermal depot medication and explants

BI= buprenorphine implant; US= United States of America; USD= US dollar.

Table A6: Strengths and Limitations of Guidelines using AGREE II16

Strengths	Limitations
Australia National Guidelines for Medication-Assisted Treatment of Opioid Dependence, Gowing, 201427	
- Clearly defined objectives, scope and target populations - Guideline was developed based on existing guidelines (four separate documents) and systematic review - Recommendations explicitly linked to supporting evidence - Recommendation was clearly presented	- Conflicts of interest not clearly described - Patient views and preferences not clearly described - Guideline update plan not described

Appendix 4: Main Study Findings and Author's Conclusions

Table A7: Summary of Findings of Included Studies

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td colspan="2">RCTs</td></tr>
<tr><td colspan="2">Lintzeris, 2013[17]</td></tr>
<tr><td>
Comparison of BN-F vs BN-T in patients with opioid addiction:
<u>Dose effects during Double-blind Assessment:</u>
<table>
<tr><th>Outcome</th><th></th><th colspan="2">After Double-blind assessment (Day 17)</th><th>P value</th></tr>
<tr><th></th><th>Baseline (n=92)</th><th>BN-F (n=43)</th><th>BN-T (n=45)</th><th></th></tr>
<tr><td>Pre-dose SOWS (0-64)</td><td>5.1 (6.7)</td><td>4.2 (6.7)</td><td>5.4 (7.7)</td><td rowspan="6">NR</td></tr>
<tr><td>Pre-dose OOWS (0-10)</td><td>0.6 (0.9)</td><td>0.2 (0.7)</td><td>0.6 (1.0)</td></tr>
<tr><td>Self-reported cravings (0-100)</td><td>6.1 (13.0)</td><td>5.4 (9.8)</td><td>3.5 (8.1)</td></tr>
<tr><td>Pre-dose sedation (0-100)</td><td>7.0 (12.6)</td><td>8.1 (13.3)</td><td>3.6 (6.1)</td></tr>
<tr><td>Post-dose sedation (0-100)</td><td>10.1 (17.1)</td><td>11.5 (17.7)</td><td>6.0 (13.4)</td></tr>
<tr><td>Feeling "high" (0-100)</td><td>10.6 (18.6)</td><td>9.4 (15.3)</td><td>5.0 (9.2)</td></tr>
</table>
<u>Adverse Effects:</u>
- No significant differences between number of side effects experienced by patients in either group before double-blind phase
<u>Substance Use and other Clinical Outcomes:</u>
- No significant differences observed between BN-T and BN-F groups on urine drug screen results or self-reported proportion of days using opioids, amphetamines, cannabis, benzodiazepines or alcohol.
- No significant differences between tablets and film in WHOQOL-BREF.
<u>Dissolution time and removal of film:</u>
- Significant difference (p=0.007, F=7.668) in mean dissolution time in open-label phase (Day 18-31) between BN-F (173 ±71 s) and BN-T (242 ±141 s) groups.
- Moderate correlation (r=0.41(42), p(two-tailed)<0.01) between daily dose and mean dissolution time in BN-T group.
- No correlation (r=0.20(38), p(two-tailed)=0.20) between daily dose and mean dissolution time in BN-F group.
- No difference in dissolution time with increasing number of films.
- Ability to remove film (wholly or partially) related to number of films dosed, with more participants able to remove film when more than two films were dosed at same time.
- No patients administered one film was able to remove after 30 seconds.
</td><td>
- BN-F comparable to existing BN-T preparation with regard to dose effect, patient preferences, adverse effects, plasma levels and global clinical outcomes
- BN-F appears to better reduce risk of diversion as well as time required for supervised dosing due to its decreased dissolution time and reduced ability to remove film after administration
</td></tr>
<tr><td colspan="2">Rosenthal, 2013[18]</td></tr>
<tr><td>
Comparison of BI vs. PI + BN-T vs BN-T (open-label) in patients with opioid addiction:
<table>
<tr><th>Outcome</th><th>BI (N=114)</th><th>PI + BN-T (N=54)</th><th>BN-T (open-label) (N=115)</th><th>P-value (BI vs PI + BN-T)</th><th>P-value (BI vs BN-SLT)</th></tr>
<tr><td>Mean CDF of % urines opioid-negative, weeks 1-24</td><td>36.0</td><td>14.4</td><td>35.1</td><td><0.0001</td><td>0.81</td></tr>
<tr><td>Mean CDF of % urines opioid-negative, weeks 1-16</td><td>39.6</td><td>17.9</td><td>37.8</td><td><0.0001</td><td>0.65</td></tr>
</table>
</td><td>
- Buprenorphine implants resulted in significantly higher opioid-negative urine screening, higher retention rates, and lower clinician and patient-rated withdrawal compared with placebo amongst opioid-dependent patients
- Buprenorphine implants are non-inferior to sublingual buprenorphine-naloxone tablets in management of opioid-
</td></tr>
</table>

Main Study Findings	Author's Conclusion

Mean CDF of % urines opioid-negative, weeks 17-24	28.9	7.2	29.6	<0.0001	0.86
Proportion of study completers, N (%)	73 (64.0)	14 (25.9)	76 (63.9)	0.0002	0.62
Mean COWS over 24 weeks (0-100)	2.49	4.52	1.71	<0.0001	0.0005
Mean SOWS over 24 weeks (0-100)	5.30	8.42	2.83	<0.0001	0.0006
Mean VAS-opioid craving over 24 weeks (0-100)	10.2	21.8	7.1	<0.0001	0.054

Non-inferiority comparison of BI versus BN-T (open-label)

- Unadjusted mean (95% CI) proportion of opioid-negative urine screenings with and without imputation based on self-report: 31.2% vs 33.5% (27.3, 39.6); CI for the difference of proportions (-10.7, 6.2)

Treatment exposure of BI versus PI + BN-T (open-label)

- Median (mean: range) number of weeks of implant exposure (before removal): 25.0 (26.9; 4-60) vs 15.5 (18.4: 1-56)
- Proportion of those receiving additional implants: 21.9% (25/114) vs 38.8% (21/54)

Rescue Medication

- Patients in BI arm requiring rescue sublingual buprenorphine-naloxone: 39% (45/114);
- Mean days of RM used per week: 0.10; mean mgs per week: 0.91

Adverse Events of BI vs PI + BN-T vs BN-SLT (open-label)

- Patients with at least 1 AE: 67.5% (77/114) vs 61.1% (33/54) vs 71.4% (85/119)
- Patients with serious AEs: 5.3% (6/114) vs 5.6% (3/54) vs 5.9% (7/119)
- Implant-site reactions: 27.2% (31/114) in BI vs 25.9% (14/54) in PI; most commonly hematomas (7.0% vs 11.1%) and pain (5.3% vs 9.3%)
- No significant differences between groups on any AEs
- No evidence of unscheduled implant removal or attempted removal
- One death in study occurring in BN-SLT group, due to accidental overdose three days following discontinuation from study, initiated by subject

dependence

Gunderson, 2016[25]

Retention into treatment on Days 3, 15 and 22, BN-HBT vs BUP

	Retention, Number (%)		Between-Group Difference, %		
	BN-HBT (N=383)	**BUP (N=375)**	**Estimate**	**95% CI**	**P-value**
Per protocol					
Day 3	309/329 (93.9%)	302/326 (92.6%)	1.3 (1.96)	-2.6 to 5.1	0.512
Day 15	273/329 (83.0%)	269/326 (82.6%)	0.5 (2.95)	-5.3 to 6.3	0.875
All patients					
Day 3	357/383 (93.2%)	344/375 (91.7%)	1.5 (1.92)	-2.3 to 5.2	0.440
Day 15	287/383 (74.9%)	279/375 (74.4%)	0.5 (3.16)	-5.7 to 6.7	0.866
Day 22 *cross-over	262/383 (68.4%)	262/375 (69.9%)	NR	NR	NR

Opioid Withdrawal Symptoms of BN-HBT vs generic BUP

- Least squares mean AUC value of COWS days 1-15: 5.4 vs. 5.53
- Between-group difference (COWS): -0.10 (95% CI, -0.54 to 0.34)

- Non-inferiority established between higher-bioavailability sublingual buprenorphine-naloxone tablet formulary and generic buprenorphine during induction and early stabilization
- Treatment retention rates were similar between groups at day 3, 15 and 22
- No significant difference in adverse effects between groups

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td>

- Least squares mean AUC value of SOWS days 1-15: 11.17 vs 11.25
- Between-group difference (SOWS): -0.07 (95% CI -1.33 to 1.18)

Adverse Events of BN-HBT vs generic BUP

- Patients with at least 1 AE: 15.9% (61/383) vs 14.7% (55/375); no significant differences between groups
- Proportion of patients reporting AE in open-label phase: 11.8% vs 10.9% (P=0.67)
- Most common reported AEs (all patients): constipation (3.1%), headache (1.7%)
- Four patients in BUP group discontinued due to AE (nausea, diaphoresis, flushing, stomach cramps) and two in BN-HBT group (lethargy and vomiting, constipation)

</td><td></td></tr>
<tr><td colspan="2">Rosenthal, 2016[20]</td></tr>
<tr><td>

Comparison of BI vs BN-T in opioid-dependent patients (number/total (%)):

Outcome	BI (N=84)	BN-T (N=89)	Difference % (95% CI)	P-value
At least 4 months opioid-negative urine samples + self-reports	81/84 (96.4%)	78/89 (87.6%)	8.8 (0.009 to ∞)	<0.001
Cumulative 6 months opioid-negative urine samples + self-reports	72/84 (85.7%)	64/89 (71.9%)	13.8 (0.018 to 0.258)	0.03
At least 4 months opioid-negative urine samples + self-reports, all imputed results as positive	78/87 (89.7%)	76/89 (85.4%)	4.3 (-0.055 to 0.140)	0.39
Cumulative 6 months opioid-negative urine samples + self-reports, all imputed results as positive	70/87 (80.5%)	60/89 (67.4%)	13.0 (0.002 to 0.259)	0.049
Cumulative 6 months opioid-negative urine samples + self-reports, all imputed results positive and supplementary sublingual tablet use as nonresponders	55/87 (63.2%)	48/89 (53.9%)	9.3 (-0.052 to 0.238)	0.21

- Number needed to treat opioid-dependent patients to have at least 4 months opioid-negative urine samples + self-reports with BI vs BN-T: 11.36
- Number needed to treat opioid-dependent patients to have a cumulative 6 months opioid-negative urine samples + self-reports with BI vs BN-T: 7.25

Dose effects (mean change (SD))

Outcome	BI (N=84)	BN-T (N=89)	Difference % (95% CI)	P-value
Baseline to end of treatment change in COWS	-0.1 (1.51)	-0.1 (1.69)	-0.0	0.92
Baseline to end of treatment change in SOWS	-0.6 (4.63)	0.1 (5.26)	-0.6	0.43
Requiring supplemental sublingual buprenorphine (number/total %)	15/84 (17.9%)	13/89 (14.6)		0.56

Supplementary Medication

- Patients requiring rescue sublingual buprenorphine-naloxone in BI arm vs BN-T arm: 17.9% (15/84) vs 14.6% (15/89), p>0.05

Adverse Effects of BI vs BN-T

- Patients with at least 1 AE: 48.3% (42/87) vs 52.8% (47/89)
- Patients with serious AEs: 2.3% (2/87) (convulsions, worsening bipolar I disorder) vs 3.4% (3/89) (biliary colic, chronic cholecystitis, bronchitis)
- Patients with at least 1 implant-site related AE: 23.0% (20/87) vs 13.5% (12/89)
- One patient in BI arm discontinued due to adverse events (muscle spasms)
- Study not powered to detect differences in adverse events

</td><td>

- Buprenorphine implants did not result in an inferior likelihood of maintaining opioid-negative urine samples and self-reports
- Study population had exceptionally high response in control group
- May need to broaden population to assess efficacy vs sublingual tablets in other settings

</td></tr>
</table>

Main Study Findings	Author's Conclusion

Webster, 2016[21]

Comparison of BN-HBT vs BUP in opioid-dependent patients

Retention into treatment on Day 3

	Retention, Number (%)		Between-Group Difference, %	
	BN-HBT (N=155)	**BUP (N=155)**	**95% CI**	**P-value**
Per protocol				
Day 3	113/128 (88.3%)	122/128 (95.3%)	-13.7 to -0.4	0.040
Full analysis				
Day 3	132/155 (85.2%)	147/155 (94.8%)	NR	NR

- 235 of 256 (91.8%) patients in the per-protocol sample were retained at day 3
- Patents not retained at day 3 BN-HBT vs generic BUP: 20/155 (12.9%) vs 7/155 (4.5%)
- Reasons for withdrawal during induction phase: protocol driven (BN-HBT=5; BUP=1); lost to follow-up/requested discontinuation (BN-HBT=7; BUP=2); withdrawn by investigator for non-compliance with study procedures (BN-HBT=7; BUP=4); AEs (BN-HBT=2); not withdrawn but no day 3 dosing (BN-HBT=2; BUP =1);
- No patient met criteria for precipitated withdrawal (increase in COWS baseline score at the 0.5 and 1.5 hour post-dose on day 1

Opioid Withdrawal/Cravings

- Mean (±SD) improvements from baseline in COWS total scores for overall sample, BN-HBT induction group, and BUP induction group into maintenance phase (Day 4): -8.9 ± 5.8, -9.4 ± 5.8, and -8.5 ± 5.7
- Mean (±SD) improvements from baseline in COWS total scores for overall sample, BN-HBT induction group, and BUP induction group to end of maintenance phase (Day 29): -11.9 ± 5.3, -12.5 ± 5.2, and -11.4 ± 5.4
- Mean (±SD) improvements from baseline in SOWS total scores for overall sample, BN-HBT induction group, and BUP induction group into maintenance phase (Day 4): -21.6 ± 15.1, -24.7 ± 16.0, and -18.9 ± 13.8
- Mean (±SD) improvements from baseline in SOWS total scores for overall sample, BN-HBT induction group, and BUP induction group to end of maintenance phase (Day 29): -27.2 ± 15.3, -30.4 ± 16.0, and -24.3 ± 14.2

AE during blinded induction phase (Days 1-3)

	BN-HBT (N=155)	BUP (N=155)	Overall (N=310)	Chi-square Test	P-value
AE	45 (29.0%)	46 (29.7%)	91 (29.4%)	0.02	0.90
Treatment-emergent AE	32 (20.6%)	38 (24.5%)	70 (22.6%)	0.66	0.42
Severe AE	3 (1.9%)	1 (0.6%)	4 (1.3%)	1.01	0.31
Severe treatment-emergent AE	2 (1.3%)	1 (0.6%)	3 (1.0%)	0.34	0.56
Serious AE	1 (0.6%)	0 (0%)	1 (0.3%)	1.00	0.32
Serious treatment-emergent AE	0 (0%)	0 (0%)	0 (0%)	NA	NA
AE leading to discontinuation	2 (1.3%)	1 (0.6%)	3 (1.0%)	0.34	0.56

- Most common AEs: nausea (8.1%), headache (7.1%), vomiting (5.2%)
- During open-label maintenance phase, 96 of 283 patients (33.9%) experienced total of 152 treatment-emergent AEs
- 3 patients (1.1%) reported severe AE considered unrelated to treatment; 2 patients (0.7%) experienced two SAEs of attempted suicide and bacteremia secondary to pyelonephritis (both determined unrelated to study medication)
- Three patients (1.1%) experienced 4 AEs resulting in study discontinuation
- No deaths occurred in either phase of study

- High-bioavailability sublingual buprenorphine-naloxone did not demonstrate non-inferiority to generic buprenorphine for patients retained into treatment on Day 3, as lower limit of 95% confidence-interval (-13.7) was ≥10%
- Rates of clinical response via COWS, SOWS and VAS of opioid craving were comparable between patients regardless of induction medication

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td colspan="2">Non-randomized studies</td></tr>
<tr><td colspan="2">Clay, 2014[22]</td></tr>
<tr><td>
Retention into treatment, discontinuation, and switch, BN-F vs BN-T
- Cases of discontinuation: 1134 vs 821
- Time to discontinuation significantly longer in BN-F group after adjustment of covariates (HR 0.818, p=0.0005)
- Retention into treatment at 6 months: 63.78% vs 58.13%; p=0.002
- Estimated probability of discontinuing treatment before 12 months via Kaplan-Meier analysis: 52.86% vs. ~58.66%
- Proportion of BN-T who switched to film: 251 (16.62%)
- Proportion of BN-F who switched to tablet: 102 (3.65%)
Resources and Healthcare Costs
Adjusted healthcare costs, resource utilization in the 12 months before and after enrolment
<table>
<tr><th rowspan="2">Resource Utilization</th><th colspan="3">12 months before enrollment</th><th colspan="3">12 months after enrollment</th></tr>
<tr><th>BN-T (N=1503)</th><th>BN-F (N=2779)</th><th>P-value</th><th>BN-T (N=775)</th><th>BN-F (N=857)</th><th>P-value</th></tr>
<tr><td>Pharmacy Claims</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mean</td><td>28.32</td><td>26.76</td><td>0.0893</td><td>33.61</td><td>32.71</td><td>0.2624</td></tr>
<tr><td>CI</td><td>24.37; 32.90</td><td>23.16; 30.92</td><td></td><td>27.65; 40.85</td><td>26.95; 39.70</td><td></td></tr>
<tr><td>Probability to have at least one hospitalization</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mean</td><td>0.34</td><td>0.3</td><td>0.004</td><td>0.23</td><td>0.19</td><td>0.0158</td></tr>
<tr><td>CI</td><td>0.30; 0.39</td><td>0.26; 0.35</td><td></td><td>0.20; 0.25</td><td>0.17; 0.22</td><td></td></tr>
<tr><td>Outpatient visits</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mean</td><td>8.74</td><td>8.93</td><td>0.2074</td><td>9.51</td><td>9.88</td><td>0.0185</td></tr>
<tr><td>CI</td><td>7.96; 9.61</td><td>8.14; 9.80</td><td></td><td>8.60; 10.52</td><td>8.95; 10.92</td><td></td></tr>
</table>
- Patients receiving film formulation had slightly higher number of outpatient visits, but a lower probability to have one hospitalization or more
</td><td>
- Patients treated with BN-F appeared to stay longer on treatment,
- BN-F group had lower probability to be hospitalized
- Unable to ascertain whether there is a causal relationship between these formulations and outcomes
- Values for resource utilization in BN-F group before enrollment should be carefully considered with results
</td></tr>
<tr><td colspan="2">Proctor, 2014[23]</td></tr>
<tr><td>
UDS and Retention rate at 6 months
<table>
<tr><th>Medication Group</th><th>UDS+ for opioids</th><th>UDS + for nonopioids</th><th>Retention (%)</th></tr>
<tr><td>Buprenorphine (BUP)</td><td>21.4%</td><td>44.6%</td><td>20.2%</td></tr>
<tr><td>Buprenorphine-naloxone (BN)</td><td>11.1%</td><td>22.2%</td><td>30.4%</td></tr>
</table>
- No significant difference on prevalence of UDS positive readings
- Retention rate for BN group (30.4%) significantly higher than BUP (20.2%) (p=0.001)
- Binary logistic regression model did not find medication group to be a significant independent predictor of retention in treatment at 6 months (R^2= 0.05)
Length of stay in treatment
- BN group had a significantly longer length of stay in treatment than BUP
- (4 months vs 2 months, n^2=0.047).
</td><td>
- No indication of superiority between BN and BUP.
- Illicit drug use rates and proportion enrolled in treatment at 6 months similar between groups
- Mean length of stay in treatment significantly longer in BN group vs BUP
- Minor advantage of BN over BUP
</td></tr>
<tr><td colspan="2">Lavonas, 2014[26]</td></tr>
<tr><td>
Changes in prescribing over time
- Number of patients filling prescriptions for sublingual buprenorphine increased 228% relative to US population
- No significant difference in prescription increase between formulations
Abuse and drug diversion (rate defined as program events per 10,000 URDD)
</td><td>
"rates of abuse and diversion of buprenorphine tablets, with or without naloxone, consistently exceed those of buprenorphine-naloxone combination film" (page
</td></tr>
</table>

Main Study Findings	Author's Conclusion
Abuse cases involving buprenorphine (Poison Center Program data) - 1,068 reports of intentional abuse of buprenorphine (including BN-F, BN-T, BUP) - Average abuse rate for BN-T was 4.1 times that of BN-F (3.7 vs. 0.9. p<0.001) Drug diversion cases involving buprenorphine (Drug Diversion Program data) - 1,374 cases of buprenorphine diversion reported (including BN-F, BN-T, BUP) - Average diversion rate for BN-T was 10.9 times that of BN-F (13.1 vs 1.4, p<0.001), consistent for all year-quarters studied - Notably, BN-T had a higher rate of diversion than BUP (14.0 vs 9.7, p<0.001) Reports of buprenorphine abuse by patients entering treatment (Patients entering Opioid Treatment Program (OTP) and Survey of Key Informants' Patients Program (SKIP)) - 4,669 patients (37.8% of all included) endorsed buprenorphine abuse in the past month - BN-T abuse rate (program was 2.2 times the BN-F rate (20.8 vs 9.5, p<0.001) Abuse of non-oral routes - 229 reports of abuse by injection or snorting during the study period (21.4% of all abuse exposure reports) - Average abuse rate reported by Poison Center Program by combination of parenteral and nasal routes 4.8 times higher in BN-T vs BN-F (0.9 vs 0.2, p<0.001) - Average abuse rate by both OTP and SKIP programs by parenteral route only was 3.7 times higher in BN-T group (3.7 vs 1.6, p<0.001) - Total of 1,186 patients reported injecting BN-T "to get high" in the 30 days prior to entering treatment programs (25.4% of all buprenorphine sublingual abuse endorsements)	33)
Economic studies	
Carter, 2017[29]	
Abstinence and retention into treatment (12-month modeled time horizon) - Higher rates of complete abstinence in BI compared to BN-T group (75% vs 54%) and retention in treatment (78% vs 58%)	*"The outcomes of this model support buprenorphine implants for opioid dependent, clinically stable adults. This stable patient subgroup only comprises a portion of the treated opioid use disorder population, but the benefits of buprenorphine implants in this subgroup might translate into a re-distribution of resources to more effectively treat other subgroups."* (page 6)

	BI	BN-T	Difference
Direct Medical Costs	$19,367	$22,031	-$2,665
- Acquisition	$9,414	$2,922	$6,492
- Administration	$864	$1,101	-$237
- Diversion	$0	$250	-$250
- Supplemental Use	$54	$37	$18
- Emergency Room and Hospitalization	$8,444	$16,484	-$8,0.04
- Rehabilitation Services	$591	$1,152	-$563
- Pediatric poisonings	$0	$9	-$9
Non-Medical Costs	$1,367	$3,088	-$1,721
- Criminal Justice	$1,265	$2,476	-$1,212
- Lost Wages, Productivity and OOP costs	$102	$612	-$510
Base Case Summary Outcomes			
Total Costs	$20,733	$25,119	-$4,386
Abstinent Patients	751	537	214
Retained Patients	776	577	199
QALYs	0.832	0.801	0.031

- At a base case willingness-to-pay (set at $50,000 per QALY), BI was associated with an incremental net monetary benefit of $5,953 ($20,812 (20,689-20,935 CI) vs $15,0999 (14,778-15,420 CI) p<0.05)
- In PSA with 1,000 iterations to assess model uncertainty, BI was cost-effective in 89% of the iterations and dominant in 84%

Main Study Findings		Author's Conclusion
Guidelines		
Australia National Guidelines for Medication-Assisted Treatment of Opioid Dependence, Gowing, 2014[27]		
Recommendations	Level of Evidence	Grade of recommendations
"A film preparation of buprenorphine-naloxone became available in Australia (the tablet formulation is scheduled to be removed from the market in 2013). It is easier to supervise administration of the film preparation, compared to tablets (Lintzeris et al. 2013), making this preparation less likely to be diverted" (pg. 82)	NR	NR

AE= adverse events; AUC=area under the curve; BI= buprenorphine implant; BN-F= buprenorphine-naloxone sublingual film; BN-HBT= buprenorphine-naloxone high-bioavailability sublingual tablet BN-T= buprenorphine-naloxone sublingual tablet; BUP= sublingual buprenorphine (generic); CDF= cumulative distribution functions; CI= confidence interval; COWS= Clinician Reports of Withdrawal Symptoms; ER= emergency room; ITT= intention-to-treat; NR= not reported; OOP= out-of-pocket; OOWS= Objective Opioid Withdrawal Scale; OUD= opioid use disorder; PSA= probabilistic sensitivity analysis; QALY= quality-adjusted life years; RCT= randomized controlled trial; SD=standard deviation; SOWS= Subjective Opioid Withdrawal Scale; WHOQOL-BREF= World Health Organization Quality of Life Brief; UDS= urine drug screening; UDS+= positive urine drug screening; URDD= unique recipients of dispensed drug; VAS= visual analog scale.